



# Lecture 4: Prostatic Hyperplasia and Prostate Cancer



## Objectives:

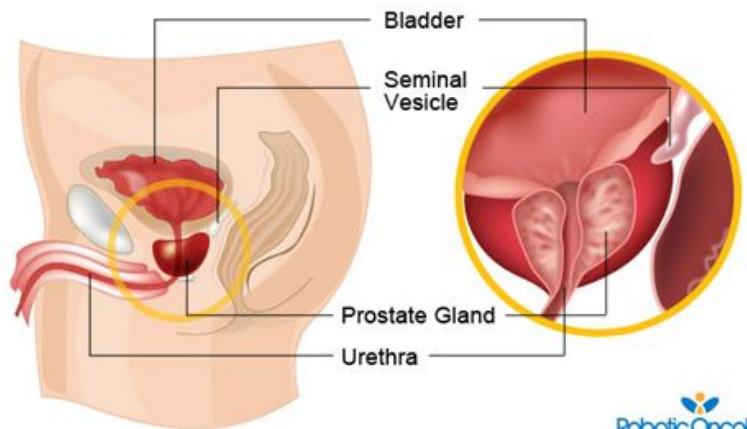
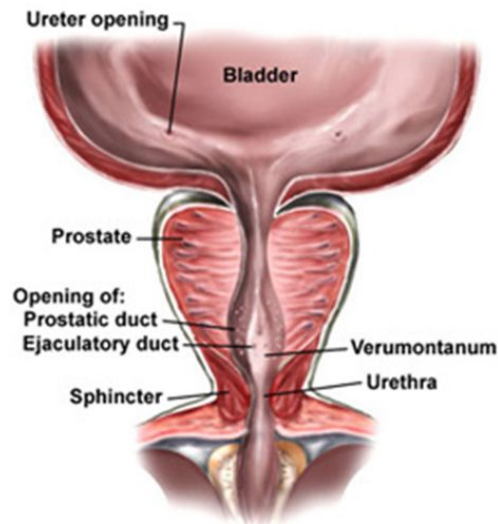
- Understand the basic anatomical relations and zones of the prostatic gland.
- Know the epidemiology, pathogenesis and histopathologic features of benign prostatic hyperplasia and carcinoma of the prostate.

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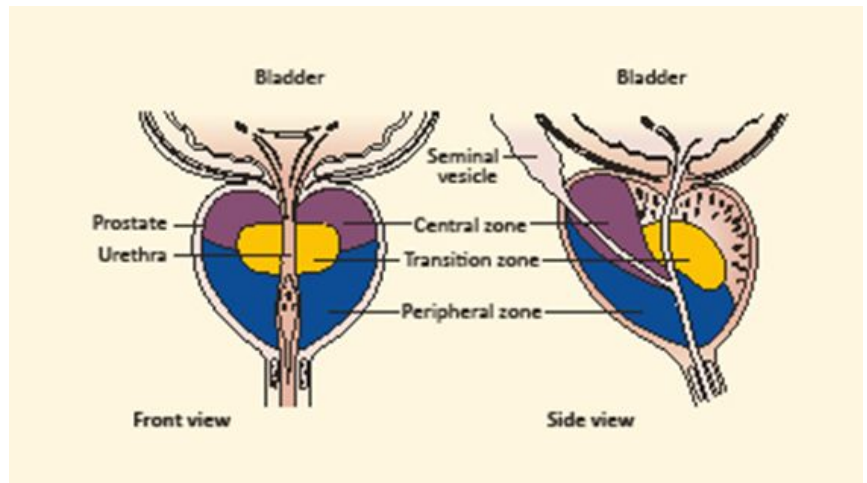


**Important**  
**Terminology**  
**Doctor's Notes**  
Extra Information

# Normal Prostate Anatomy and Histology



Robotic Oncology



## Prostate Anatomy

Prostate weighs 20 grams in normal adult.

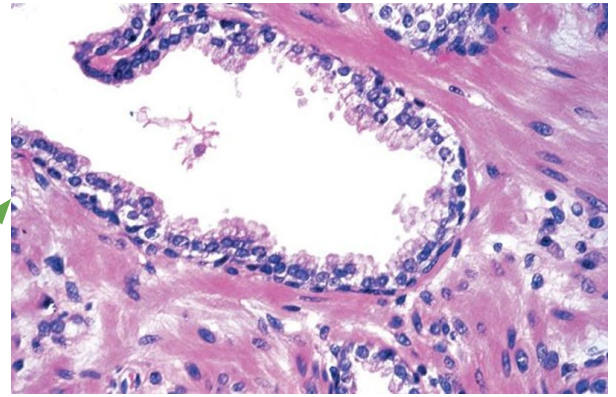
- Retroperitoneal organ, encircling the neck of bladder and urethra.
- Devoid of a distinct capsule.
- The prostate is divided into different zones. They are Central, Peripheral and Transitional zones.
- **The transition zone is the middle area of the prostate, between the peripheral and central zones. It surrounds the urethra as it passes through the prostate.**
- **The majority of prostate cancers are found in the peripheral zone and benign nodular hyperplasia in the transitional zone.**

# Normal Prostate Anatomy and Histology

## Prostate Histology

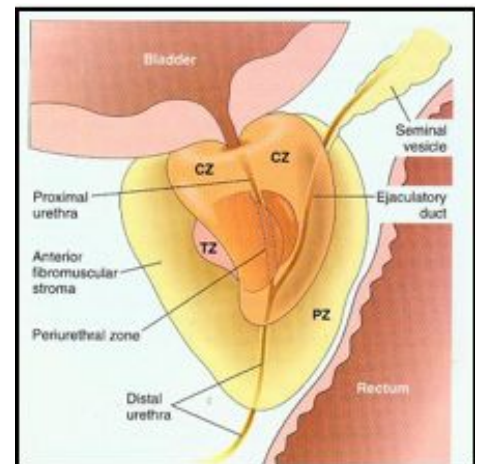
- Microscopically the prostate is a tubulo-alveolar organ. The prostate glands are lined by **two layers of cells, basal cells and columnar secretory cells.**

Good amount of cytoplasm, clear nucleus, on a basal layer. In cancers the basal layer is lost. The nucleus is darker, and less cytoplasm



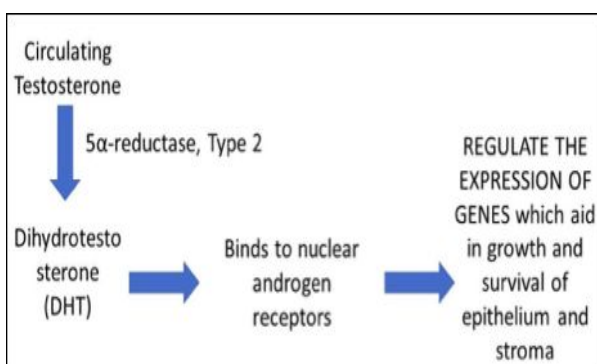
## Benign Prostatic Hyperplasia (BPH)

- Also known as benign nodular hyperplasia.
- Extremely common lesion in men over age 50.
- About 20% men have BPH by age 40
- About 70% men have BPH by age 60
- **About 90% men have BPH by age 80.**
- Hyperplasia of glands and stroma results in large nodular enlargement in the **periurethral region of the prostate.**
- Once the nodules become large they compress the prostatic urethra causing either partial, or complete obstruction of the urethra.
- Nodular hyperplasia is **not** a premalignant lesion.



## BPH: Pathogenesis

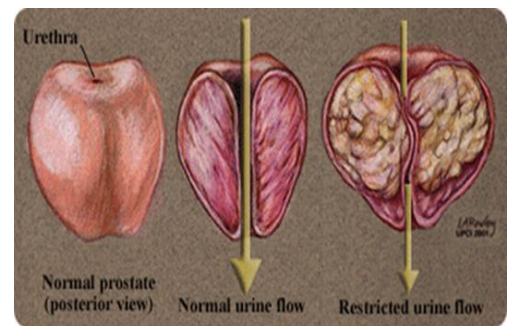
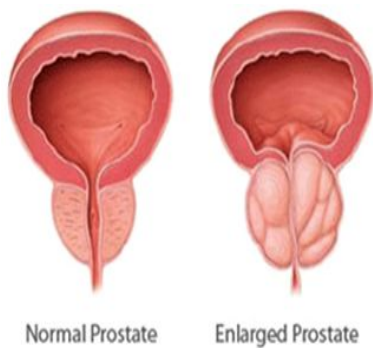
- The essential cause of BPH is unknown.
- The pathogenesis is related to the action of androgens.
- **Dihydrotestosterone (DHT) is the ultimate mediator for prostatic growth.** It increases the proliferation of stromal cells and inhibits epithelial cell death. Therefore DHT is implicated in the pathogenesis of both benign prostatic hyperplasia (BPH) and prostate cancer.



- Testosterone is converted to dihydrotestosterone (DHT) by 5-alpha reductase enzymes.
- Drugs that act as inhibitors of 5-alpha reductase, therefore have an important role in the prevention and treatment of BPH and prostate cancer.
- Prepubertal castration prevents BPH.

## BPH: Gross Morphology

- The prostate weighs between 60 and 100 grams.
- The hallmark of BPH is nodularity due to glandular and fibro-muscular proliferation.
- Nodular hyperplasia begins in the inner aspect of the prostate gland, the transition zone.
- Cut-section shows nodules which vary in size, color and consistency depending on which element is proliferating more (glandular or fibro-muscular).
- It compresses the wall of the urethra resulting in a slit-like orifice.

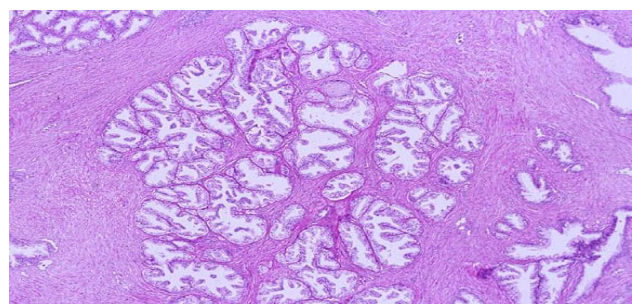
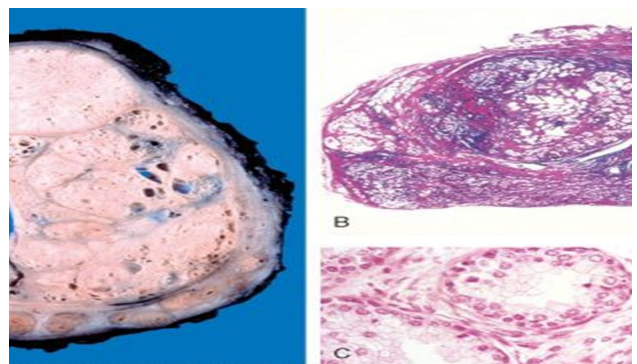
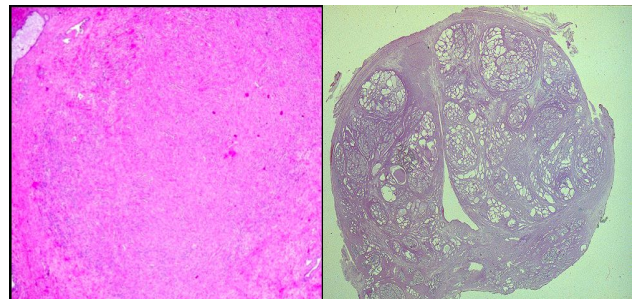


## BPH: Microscopy

- Microscopically, the main feature of BPH is **nodularity**
- The nodules can be:
  1. Purely stromal nodules composed mainly of fibromuscular elementOR
  2. Fibroepithelial with both glandular and fibromuscular component.

The nodules could be composed of both components

There is aggregation of small to large to cystically dilated glands, lined by two layers of epithelium surrounded by fibromuscular stroma.

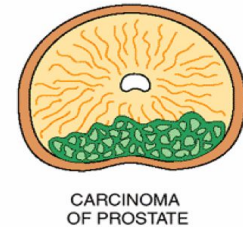
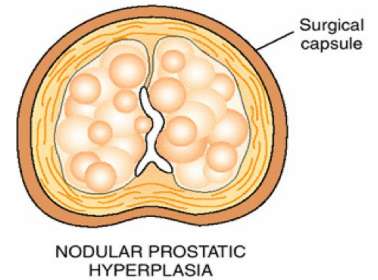
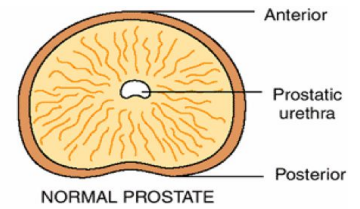


- Needle biopsy doesn't sample the transitional zone where BPH begins and occurs, therefore the diagnosis of BPH cannot be made on needle biopsy. **Needle biopsy is useful for ruling out cancer**

Nodular hyperplasia

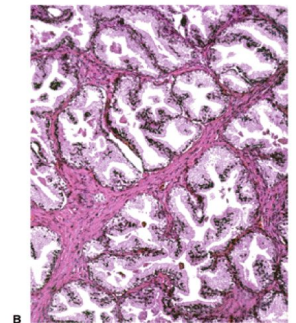
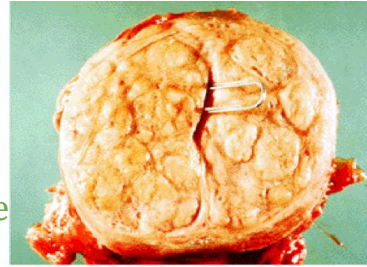
## BPH: Clinical Features

- The nodule compress the prostatic urethra → urethral obstruction leads to **retention** of urine in the bladder → bladder hypertrophy.
- The inability to empty the bladder completely leads to increase volume of residual urine therefore infection. (increased risk of UTI)
- UTI is not a normal event in males
- Increased urinary frequency.
- Nocturia.
- Difficulty in starting and stopping the stream of urine.
- Dysuria.
- Some patients present with acute urinary retention.



## BPH: Treatment

- Mild cases of BPH → may be treated with  $\alpha$ -blockers and 5- $\alpha$ -reductase inhibitors.
- Moderate to severe cases → require transurethral resection of the prostate (TURP). Removing the part of the prostate surrounding the urethra



## Prostatic Adenocarcinoma (PA):

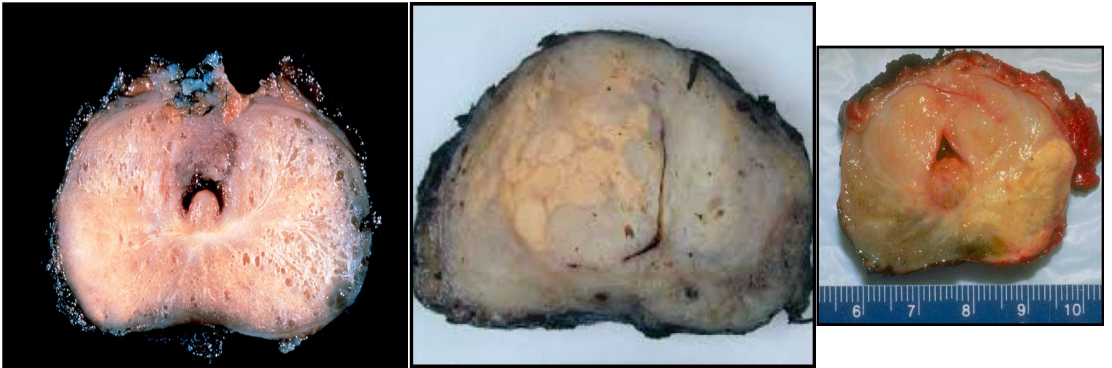
- The **most common form** of cancer in men.
- *Disease of men over age 50.*
- More prevalent among African Americans.
- These tumors show a wide range of clinical behaviors.
- Etiology: Risk factors: Age, race, family history, hormone level (androgens), environmental influences, and acquired somatic mutations.
- **Androgens** are believed to play a major role in the pathogenesis.

### Metastasis

- Metastases first spread via lymphatics: initially to the obturator nodes and eventually to the para-aortic nodes.
- **Hematogenous** extension occurs chiefly to the **bones**. Bone metastasis particularly to the axial skeleton, is frequent late in the disease and is typically osteoblastic (bone-producing) commonly to the **vertebra**.

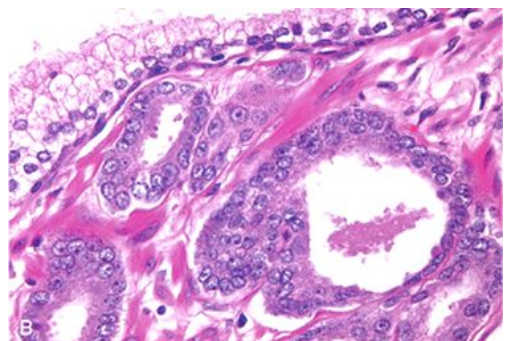
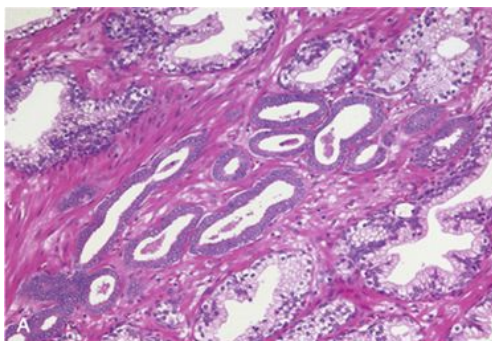
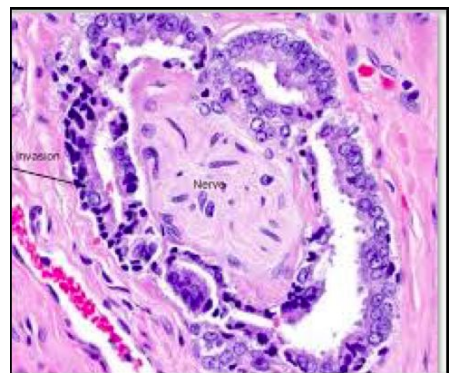
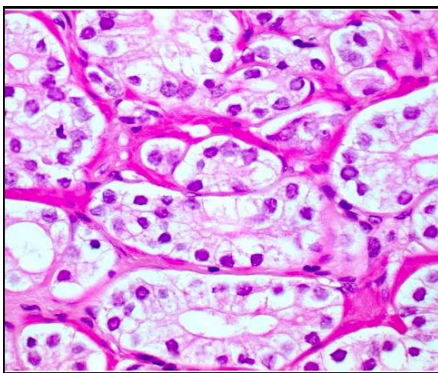
## Info

- 70% arises in the peripheral zone of the posterior part of the gland.
- Tumor is firm, gray-white, gritty and is palpable on rectal exam.
- Spread by direct local invasion and through blood stream and lymphatics.
- Local extension most commonly involves the periprostatic tissue, seminal vesicles and the base of the urinary bladder (leading to ureteral obstruction).



## Microscopically

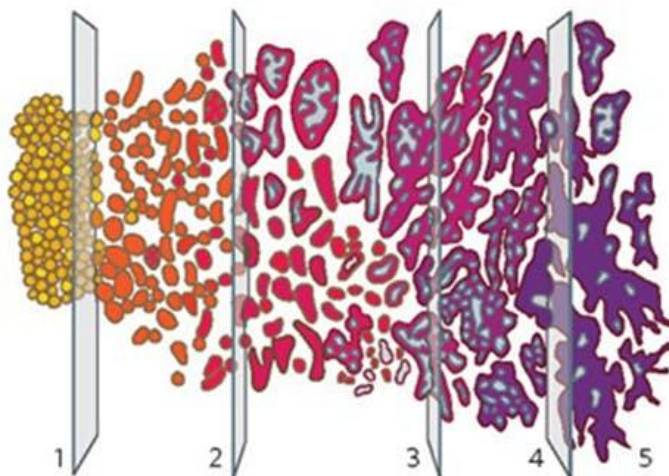
- Most lesions are adenocarcinomas that produce well-defined gland patterns.
- The malignant glands are lined by **a single layer of cuboidal** or low columnar epithelium with large nuclei and one or more large nucleoli.
- Nuclear pleomorphism is not marked.
- **The outer basal cell layer typical of benign glands is absent.**
- Commonly there is perineural invasion.



# Grading Prostatic Adenocarcinoma: Gleason Grading & Scoring

- **Gleason system** is a histological grading and scoring system for prostatic adenocarcinoma done on the **microscopic** level.
- There are **five** grades (1 to 5) depending on the degree and pattern of differentiation as seen microscopically (in which they range from, grade 1= well-differentiated to grade 5= very poorly differentiated).
- Prostate carcinomas usually have **more than one type of grade** in the tumor mass.
  - **Boy's slides:** The **two most common types** of grades seen in the biopsy for each cancer patient are added and the final sum is called the Gleason score.
  - **Girl's slides:** The **most common type** and **the most aggressive** of grades seen in the are added and the final sum is called the Gleason Score (most common & second most common on resection).
- **Doctor's note:** The **most common grade + the highest grade = Gleason score.**
- Gleason Grading and Scoring in prostate cancer is very useful in predicting prognosis of a patient.

## GLEASON PROSTATE GRADE SCALE



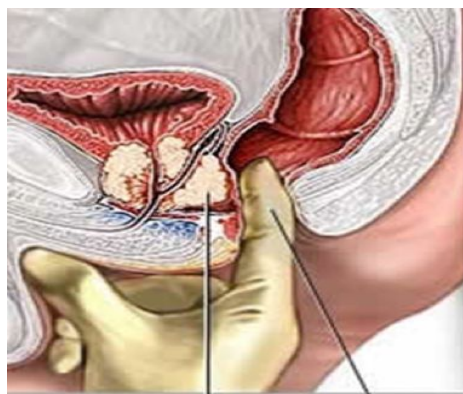
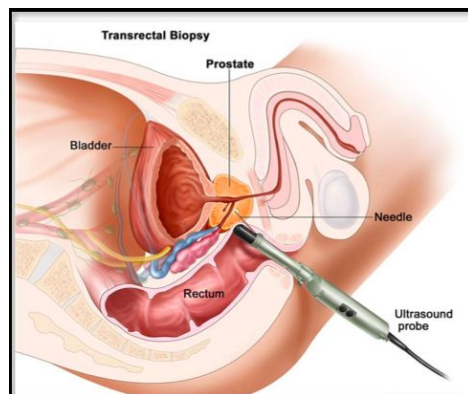
(extra picture)

## Staging Prostatic Adenocarcinoma

- Staging in prostate cancer depends on the **TNM** system (**Tumor size, lymph Node involvement, Metastases**).
- **It is the most important indicator of prognosis.**

# Prostatic Adenocarcinoma: Clinical Features

- **Microscopic** (or very small size) cancers are **asymptomatic** and are discovered incidentally.
- Most arise in the **peripheral zone**, away from urethra and therefore the urinary symptoms occur late.
- Occasionally patients present with **back pain** caused by **vertebral metastases**.
- Careful digital rectal examination may detect some **early** cancers.
- **PSA (Prostate Specific Antigen)** levels are important in the diagnosis and management of prostate cancer. However, a minority of prostate cancers may have low PSA.
- PSA is **organ specific** but **NOT** cancer specific because it could be increased in **BPH** and **prostatitis**.
- A **transrectal needle biopsy is required** to confirm the diagnosis. **Many different biopsies are taken from different areas of the prostate**

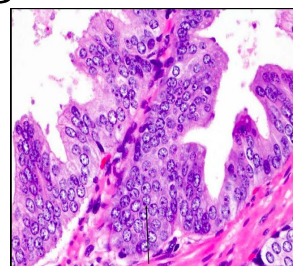


## Prostatic Adenocarcinoma: Treatment

- Surgery, radiotherapy and hormonal therapy.
- 90% of treated patients are expected to live for 15 years. **Prognosis is good**
- Currently the most acceptable treatment for clinically localized cancer is **radical surgery**.
- **Locally advanced cancers** can be treated by **radiotherapy** and **hormonal therapy**. Hormonal therapy (Anti-androgen therapy) can induce remission.
- **Advanced, metastatic carcinoma** is treated by **androgen removal treatment**, either by **orchiectomy** or by **hormonal anti-androgen therapy**.
- Metastases **first spread** via lymphatics: **initially** to the **obturator nodes** and **eventually** to the **para-aortic nodes**
- Hematogenous extension occurs chiefly to the **bones**. The bony metastasis are typically **osteoblastic in nature**.
- The prognosis depends on the Gleason score and stage of tumor.

## Prostatic Intraepithelial Neoplasia (PIN):

- PIN is the **precursor** lesion for invasive carcinoma. **Maintenance of the basal layer with the presence of atypia.**
- It can be **low grade PIN** or **high grade PIN**. (high grade PIN is like carcinoma in situ)
- PIN like prostatic carcinoma occurs in the **peripheral zone**.





# Pathoma Overview

## PROSTATE

### 1. BASIC PRINCIPLES

- a. Small, round organ that lies at the base of the bladder encircling the urethra
- b. Sits anterior to the rectum; posterior aspect of prostate is palpable by digital rectal exam (DRE).
- c. Consists of glands and stroma
  - i. Glands are composed of an inner layer of luminal cells and an outer layer of basal cells; secrete alkaline, milky fluid that is added to sperm and seminal vesicle fluid to make semen.
  - ii. Glands and stroma are maintained by androgens.

### 2. BENIGN PROSTATIC HYPERPLASIA (BPH)

- a. Hyperplasia of prostatic stroma and glands
- b. Age-related change (present in most men by the age of 60 years); no increased risk for cancer
- c. Related to dihydrotestosterone (DHT)
  - i. Testosterone is converted to DHT by 5 $\alpha$ -reductase in stromal cells.
  - ii. DHT acts on the androgen receptor of stromal and epithelial cells resulting in hyperplastic nodules.
- d. Occurs in the central periurethral zone of the prostate
- e. Clinical features include
  - i. Problems starting and stopping urine stream
  - ii. Impaired bladder emptying with increased risk for infection and hydronephrosis
  - iii. Dribbing
  - iv. Hypertrophy of bladder wall smooth muscle; increased risk for bladder diverticula
  - v. Microscopic hematuria may be present.
  - vi. Prostate-specific antigen (PSA) is often slightly elevated (usually less than 10 ng/ mL) due to the increased number of glands; PSA is made by prostatic glands and liquefies semen.
- f. Treatment
  - i.  $\alpha$ 1-antagonist (e.g., terazosin) to relax smooth muscle
    1. Also relaxes vascular smooth muscle lowering blood pressure
    2. Selective  $\alpha$ -1a antagonists are used in normotensive patients to avoid  $\alpha$ -1b effects on blood vessels
  - ii. 5 $\alpha$ -reductase inhibitor
    1. Blocks conversion of testosterone to DHT
    2. Takes months to produce results
    3. Also useful for male pattern baldness
    4. Side effects are gynecomastia & sexual dysfunction

# Pathoma Overview

## PROSTATE

### 1. PROSTATE ADENOCARCINOMA

- a. Malignant proliferation of prostatic glands
- b. Most common cancer in men; 2nd most common cause of cancer-related death
- c. Risk factors include age, race (African Americans > Caucasians > Asians), and diet high in saturated fats.
- d. Prostatic carcinoma is most often clinically silent.
  - i. Usually arises in the peripheral, posterior region of the prostate and, hence, does not produce urinary symptoms early on
  - ii. Screening begins at the age of 50 years with DRE and PSA.
    1. Normal serum PSA increases with age due to BPH (2.5 ng/mL for ages 40-49 years vs. 7.5 ng/mL for ages 70- 79 years)
    2. PSA > 10 ng/dL is highly worrisome at any age.
    3. Decreased% free-PSA is suggestive of cancer (cancer makes bound PSA).
- e. Prostatic biopsy is required to confirm the presence of carcinoma.
  - i. Shows small, invasive glands with prominent nucleoli
  - ii. Gleason grading system is based on architecture alone (and not nuclear atypia).
    1. Multiple regions of the tumor are assessed because architecture varies from area to area.
    2. A score (1- 5) is assigned for two distinct areas and then added to produce a final score (2- 10).
    3. Higher score suggests worse prognosis.
- f. Spread to lumbar spine or pelvis is common); results in osteoblastic metastases that present as low back pain and increased serum alkaline phosphatase, PSA, and prostatic acid phosphatase (PAP)
- g. Prostatectomy is performed for localized disease; advanced disease treated with hormone suppression to reduce testosterone and DHT.
  - i. Continuous GnRH analogs (e.g., leuprolide) shut down the hypothalamus (LH and FSH are reduced).
  - ii. Flutamide acts as a competitive inhibitor at the androgen receptor

# MCQ

1. Which of the following is the most important indicator for prognosis?

- A. Microscopic features
- B. Gleason Scoring
- C. Gleason Grading
- D. TNM system

2. Which of the following zones does Prostatic-Intraepithelial-Neoplasia (PIN) arise from?

- A. Transitional Zone
- B. Central Zone
- C. Urethral Zone
- D. Peripheral Zone

3. Patient came to ER, he can't pass urine. Doctor did foley's catheter. During clinical examination, doctor felt a nodules while performing PR examination. Base on previous finding, what's most likely the diagnosis?

- A. Benign prostatic hyperplasia
- B. Prostatic adenocarcinoma
- C. Normal prostate
- D. Normal seminal vesicle

4. On histologic examination the difference between benign glands and carcinoma is that:

- A. Carcinoma is smaller than benign glands, and lined by single uniform layer of cuboidal epithelium.
- B. Carcinoma is smaller than benign glands, and lined by single uniform layer of columnar epithelium.
- C. Carcinoma is larger than benign glands, and lined by single uniform layer of cuboidal epithelium.

5. Most prostate cancers arise in the:

- A. In the center of the gland
- B. In the inner gland
- C. Peripheral (outer) glands

6. What do we treat BPH mild cases with

- A.  $\alpha$ -blockers
- B. 5- $\alpha$ -reductase inhibitors
- C. Transurethral resection of the prostate (TURP)
- D. A+B

7. The essential cause of BPH

- A. The pathogenesis is related to the action of androgens
- B. Castration
- C. DHT
- D. Unknown

# Cases (from 436 team work)

1. A 67 year old man is found to have a single, hard, irregular nodule within his prostate on rectal examination. A biopsy of this lesion reveals the presence of small glands lined by a single layer of cells with enlarged, prominent nucleoli.

Q1/ From what portion of the prostate did this lesion most likely originate?

Q2/ What is the most likely diagnosis?

2. 60 years old man comes to the clinic complaining of back pain. His scan shows metastasis to the vertebrae.

Q3/ What is the most likely site of primary tumor?

Answers:

Q1) Peripheral Zone

Q2) Prostatic Adenocarcinoma

Q3) Prostate gland



## Team Members:

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## References:



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